REMARKS

I. THE CLAIMED SUBJECT MATTER IS PATENTABLE OVER THE ART

Applicants note with appreciation that the Examiner has withdrawn all prior art rejections. Accordingly, none of the above amendments are made to overcome an issue concerning the prior art.

II. CLAIMS 195-231 ARE ALLOWABLE

Applicants note with appreciation that the Examiner has indicated that claims 195-231 are allowable.

III. THE PENDING CLAIMS COMPLY WITH 35 USC §112, 1ST PARAGRAPH

The Examiner has rejected claims 154-194 and 232-240 under 35 USC §112, first paragraph, for alleged lack of enablement. Set forth below are each of the Examiner's reasons for the rejection, followed by Applicants' response.

The Examiner argues as follows:

"[T]he only agents pointed to and specifically claimed by Applicant as having agonistic activity are soluble receptors and receptors and ligands fused to antibodies...The only agents claimed as having antagonistic activity are antibodies and soluble receptors and receptors and ligands fused to antibodies. There are no teachings in the specification to indicate that any of these agents would function as claimed and the receptors and ligands are in fact claimed as having two different functions."

"The specific teachings pointed to in Wang et al. encompass only repulsive neuronal outgrowth; there are no teachings either in Wang et al. or in the instant specification that would allow one of skill to predict that angiogenesis would respond in a fashion similar to neuronal outgrowth."

"There is no specific guidance set forth in the specification to indicate that antibodies would be predictably antagonistic...Furthermore one of skill in the art, given the teachings that clustered receptors could be agonistic, would reasonably expect that at least some antibodies could have the same effect. Thus one of skill would not be able to predict...how soluble receptors, ligands, and antibodies would function."

Applicants respectfully assert that the teachings of the specification fully enable the pending claims. The application teaches, among other things, that a ligand-receptor pair of membrane proteins, EphrinB2 and EphB4, are expressed in a complementary arterial/venous pattern in vascular endothelial cells, and are required for angiogenesis. Wang et al. was cited in this prosecution merely to substantiate the assertion that Eph/Ephrin mediated signaling occurs when the extracellular domains of the Eph and Ephrin come into contact, and therefore that agents which modulate this interaction will tend to modulate angiogenesis. This mechanism of Eph/Ephrin signaling was an established dogma at the time of filing and has been repeatedly confirmed. Other references substantiating the use of an extracellular portion of an Eph or Ephrin receptor in other circumstances include Labrador et al., 1997, EMBO 16:3889-97 and Stein et al., 1998, Genes Dev. 12:667-678 (both previously cited in this prosecution). The examiner seems to suggest that the biochemical mechanism of Eph/Ephrin signaling could have been different in neural tissues than in the vascular endothelium, and that this undermines the enablement of the application. Applicants respectfully contend that this would have been an improbable assertion at the time of filing, and that the experience of the scientific community thereafter has proven the Examiner's assertion to be incorrect. It is well-known in the field of molecular and cellular biology that proteins of a conserved family tend to act by the same biochemical mechanism regardless of cellular context. G protein coupled receptors signal through G proteins, regardless of the cell in which the GPCR occurs. Cadherins are known to self-associate in a variety of different cell types. This assumption has proven so robust that exceptions are a matter of interest. Based on the teachings of any of Stein, Wang or Labrador, Applicants assert that it was well-known in the art at the time of filing that extracellular portions of Eph or Ephrin polypeptides could modulate Eph/Ephrin signaling.

It was also known in the art, and remains dogma today, that an agent that binds to an Eph or Ephrin receptor may have agonist or antagonist activities (see, e.g., Stein). Applicants assert that this does not undermine the enablement of the claims. The application discloses clear assays by which one of ordinary skill in the art may assess the agonist or antagonist activity of an agent, and further

assess the pro- or anti-angiogenic effect of an agent. Based on the teachings of the specification, one of ordinary skill in the art may design an assay to identify, e.g., Ephrin-B2 antibodies that agonize Ephrin-B2 as well as Ephrin-B2 antibodies that antagonize Ephrin-B2. It would be a matter of routine experimentation for one of ordinary skill in the art to classify antibodies or other agents as agonists or antagonists. Likewise, the teachings in the specification, combined with the ready availability of combinatorial polypeptide, antibody and small molecule libraries, allow one of ordinary skill in the art to identify a host of other agents having agonist or antagonist activity against an Eph or Ephrin with no more than routine experimentation.

Accordingly, Applicants assert that the claims as pending are fully enabled. Reconsideration and withdrawal of the rejection of the pending claims 35 USC § 112, first paragraph, is respectfully requested.

IV. CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Applicants hereby request that any fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

Date: November 19, 2003

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